Also submitted herewith are a "Clean Version of All Pending Claims" which depict the pending claims after entry of the present amendments.

REMARKS

Applicants note that the Office Action mailed July 30, 2002 set an initial three month period for response. Applicants note that submitted herewith is a Petition under 37 CFR §1.136 for a two (2) month extension of time and a check which includes the required fee. With the granting of this Petition, the time period in which to submit a timely response to the Office Action mailed July 30, 2002, will be extended to Monday, December 30, 2002.

The Form PTO-326 which accompanied the Office Action mailed July 30, 2002, indicated that claims 1 to 15 were pending, claims 1 to 5 were indicated as rejected, claim 7 was indicated as objected to and claims 6 and 8 to 15 were indicated as withdrawn from consideration.

Applicants note that claims 1, 2, 4, 5, 6 and 7 have been amended to more particularly point out and distinctly claim certain aspects of Applicants' invention. Claims 1 and 4 have been amended to focus on the use of certain inhibitors of serine protease activity of matriptase or MTSP1. Applicants submit that these amendments are clearly supported by the application as filed and give rise to no issue of new matter.

Claims 3 and 8 to 15 have been cancelled without prejudice. Applicants note that in the Office Action mailed July 30, 2002, the Examiner indicated that claims 8 to 15 were withdrawn from consideration as directed to the non-elected inventions of Groups II (claims 8 to 12) and III (claims 13 to 15). Applicants reserve their rights to file continuing and/or

divisional applications directed to subject matter deleted from the claims and to the subject matter of the cancelled claims.

Applicants note that the Office Action mailed July 30, 2001, included claim 6 as part of the invention of Group I, the group which Applicants provisionally elected. In the Office Action mailed April 4, 2002, the Examiner required election pursuant to 35 U.S.C. § 121 of a single disclosed species. In response to the Examiner's requirement of election of a single disclosed species, Applicants provisionally elected Compound 4 of Figure 1A and noted that claims 1 to 5 and 7 were readable upon the elected species. Applicants requested that the scope of examination be increased to include the genus upon finding of an allowable species. Applicants note that the Office Action mailed July 30, 2002, indicated the elected species, which was specifically claimed by claim 7, to be allowable. Since the elected species has been indicated to be allowable, Applicants submit that the scope of examination of the claims of the elected invention of Group I should properly be increased. In particular, Applicants note that claim 6, directed to another species of the elected invention, should be rejoined for examination.

The Objections

Applicants note that the Examiner objected to the specification "because Figure 1C and Table 1 are missing from the specification". Applicants note that Figure 1C was present with the application as filed. Applicants note further that the reference to "Table I" in the specification was an error.

The specification has been amended to delete reference to Table I.

With respect to the Examiner's objection to the specification because Figure 1C was said to be missing from the specification, Applicants note that Figure 1C was submitted with the present application when it was filed with the U.S.P.T.O. Submitted herewith is a copy of the Figures as originally filed and a Petition of Suzanne L. Biggs, Applicants' attorney, that they be accepted. The undersigned Applicants' attorney signed the Certificate of Express Mailing for this application when it was filed, reviewed the application and all its pages before placing it in its envelope and states that all sheets of the Figures, including Figure 1C, were in the envelope when it was mailed to the U.S.P.T.O. by Express Mail.

With regard to the Examiner's objection to claim 7 at page 3, paragraph 2.2, Applicants note that claim 7 has been amended to include the structure of Compound 4 of Figure 1A. Applicants note that claim 6 has been amended to include the structure of Compound 6 of Figure 1A.

<u>The Section 112, Second Paragraph Rejection of Paragraph 3.1, pages 3 to 4</u>

Claims 1, 2, 4 and 5 stand rejected under 35 U.S.C. §112, second paragraph as asserted indefinite (claim 3 has been cancelled).

This rejection is respectfully traversed. Applicants submit that claims 1 to 5 as originally filed were in compliance with the requirements of the Second Paragraph of Section 112. Applicants note that claims 1 and 4 have been amended to more particularly point out and distinctly claim aspects of Applicants' invention and that those claims clearly comply with the second paragraph of Section 112. Claim 2 is dependent on claim 1 and claim 5 is dependent on claim 4.

In particular, Applicants note that the Examiner objected to use of the abbreviation "MTSP1" in the claims. Applicants submit that, since the term "MTSP1" is clearly defined in the specification, the term "MTSP1" is not indefinite. Applicants note that in order to expedite prosecution of this application, claims 1 and 4 have been amended to replace "MTSP1" with "membrane-type serine protease 1".

Applicants note the Examiner rejected claim 4 as assertedly incomplete "[d]ue to lack of Figure 1C" in the specification. Applicants note that claim 4 as filed (and as pending prior to entry of the present amendments) did not refer to Figure 1C. Applicants further note that claim 3, as filed, did reference "Figure 1C"; however, claim 3 has been cancelled.

Applicants submit that the present rejection does not apply to claim 4. Should the Examiner maintain the rejection of claim 4 on this ground, appropriate clarification is requested.

Applicants submit that the rejection of claims 1, 2, 4 and 5 under 35 U.S.C. §112, second paragraph, has been overcome and request that it be withdrawn.

<u>The Section 112, First Paragraph Rejection of Paragraph 3.2.1, pages 4 to 5</u>

Claims 1, 2, 4 and 5 stand rejected under 35 U.S.C. §112, first paragraph, for asserted lack of written description.

This rejection is respectfully traversed. Applicants submit that claims 1, 2, 4 and 5, as filed, did reasonably convey to one skilled in the art that, at the time the application was filed, they were in possession of the claimed invention.

Applicants note that the claims have been amended to focus on the use of certain preferred inhibitors of MTSP1 as described

in the specification, see e.g., page 12 at lines 13 to 14. Applicants submit that clearly, they were in possession of the invention as presently claimed at the time this application was filed.

Applicants further note that the Examiner appears to object to Applicant's failure to provide biological testing data. However, Applicants do describe methods for determining the IC_{50} values for compounds to be used according to the methods of claims 1, 2, 4 and 5 (see, e.g., Example A, pages 28 to 30).

Applicants note that based on their teachings, one of ordinary skill would understand that Applicants were in possession of the claimed invention and, furthermore, could determine which compounds had an IC_{50} of 100 nM or less. Applicants submit that the Examiner's position on this grounds is not well taken.

Applicants request that the Examiner reconsider the present rejection and withdraw it.

The Section 112, First Paragraph Rejection of Paragraph 3.3, pages 5 to 7.

Claims 1, 2, 4 and 5 stand rejected under 35 U.S.C. §112, first paragraph, for asserted failure to provide enablement for treatment with any inhibitor of serine protease activity of MTSP1.

This rejection is respectfully traversed. Applicants submit that claims 1, 2, 4 and 5, as filed, were enabled.

Applicants note that claims 1, 2, 4 and 5 have been amended to focus on the use of certain preferred inhibitors of serine protease activity of MTSP1 as set forth in the specification, see e.g., page 12 at lines 13 to 14.

Applicants also note that the Examiner appears to assert Applicants' failure to provide biological activity data in the application as filed, in particular IC_{50} values, as a reason for the present rejection. Applicants submit that the Examiner's apparent position of basing this rejection on this reason is not well taken.

Applicants note that the application, as filed, would enable one of ordinary skill in the art to determine IC_{50} values for serine protease activity of matriptase or MTSP1 (see Example A) and for other serine proteases (see Example B) without undue experimentation. Using the IC_{50} values determined as described in the specification and by following the application's teachings, one of ordinary skill in the art would be able to select those compounds which inhibit serine protease activity of matriptase or MTSP1 (claim 1) or selectively inhibit serine protease activity of matriptase or MTSP1 (claim 4). (See, e.g., the specification at pages 11 to 14). Applicants note that preferably such compounds would have an IC_{50} for inhibition of serine protease activity of matriptase or MTSP1 of 100 nM or less (See, specification at page 13, lines 17 to 21). Applicants' teachings describe how to determine which compounds have an IC_{50} of 100 nM or less.

Applicants request that the Examiner reconsider this rejection and withdraw it.

Conclusion

Applicants note the Examiner's indication of the allowability of claim 7 with appreciation.

Applicants submit that in view of the foregoing claims 1, 2, 4, 5, and 7 are allowable. Applicants submit that claim 6 is allowable as well. Applicants request that the claims be allowed and passed to issue.

If a telephone interview would expedite prosecution of this application, the Examiner is encouraged to telephone the undersigned Applicants' attorney.

If the fee submitted is incorrect or if any other fee is due in connection with this response, Applicants request that Deposit Account No. 03-3975 be charged for or credited with the appropriate amount.

Respectfully submitted,
PILLSBURY WINTHROP LLP

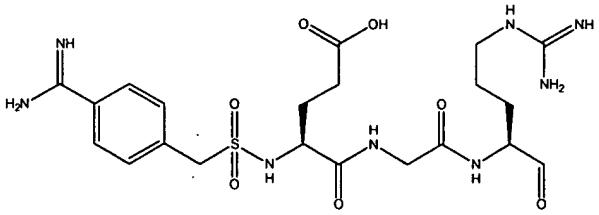
Date: December 30, 2002

By: _____
Suzanne L. Biggs
Reg. No. 30,158

11682 El Camino Real
Suite 200
San Diego, California 92130
Tel. No.: (858) 509-4095
Fax No.: (858) 509-4010

VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Amended) A method of treating a condition which is ameliorated by inhibiting or decreasing serine protease activity of matriptase or [MTSP1] membrane-type serine protease 1 in a mammal in need of treatment which comprises administering to said mammal a therapeutically effective amount of a compound which inhibits serine protease activity of matriptase or [MTSP1] membrane-type serine protease 1 wherein said compound is selected from the group consisting of:

(1) 

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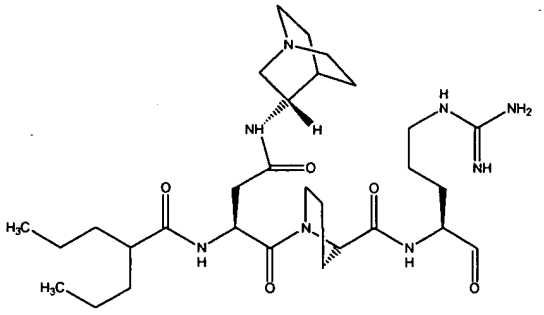
(2) 

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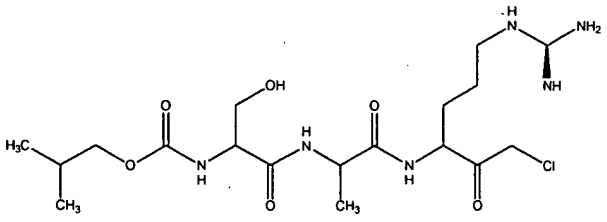
(3) 

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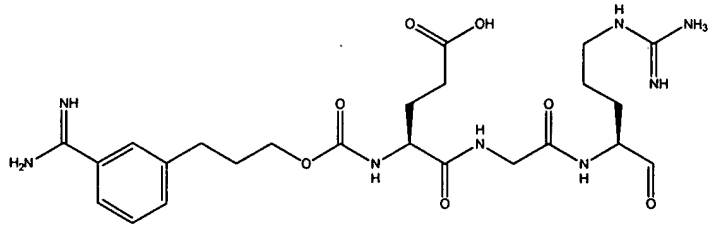

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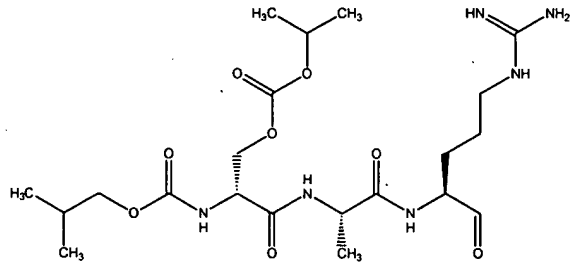

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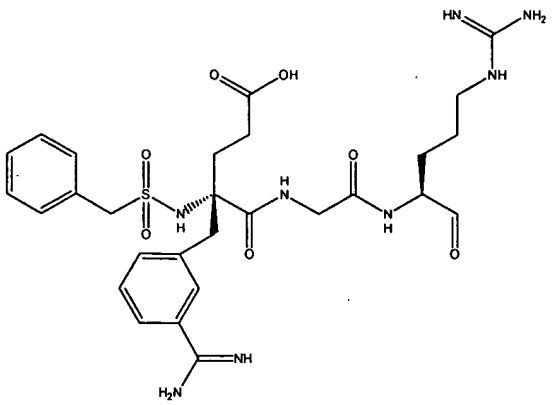

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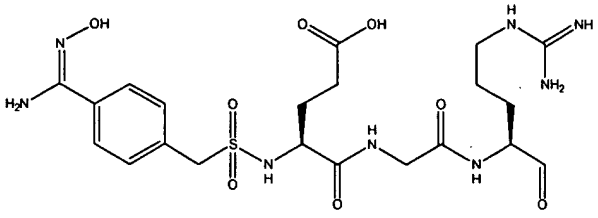

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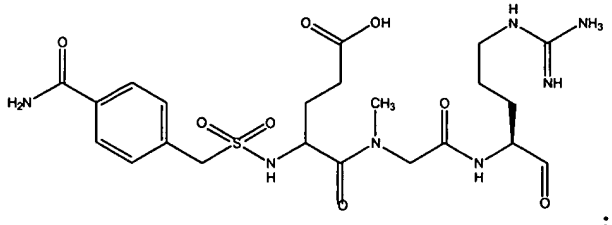

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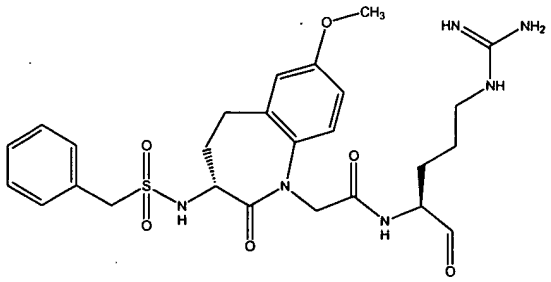

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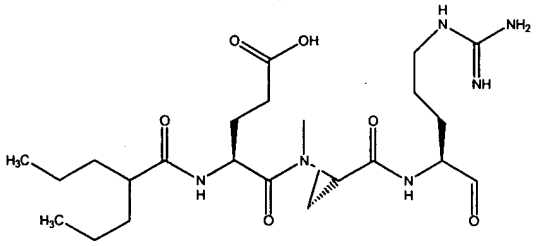

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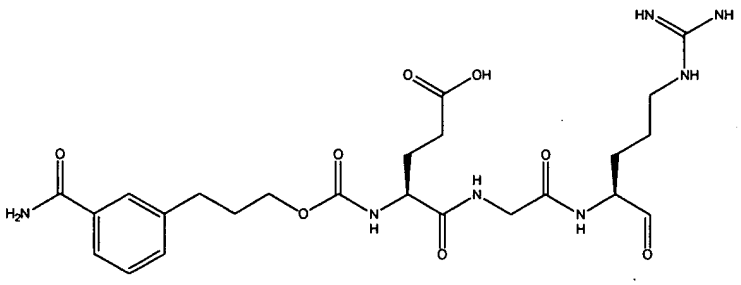

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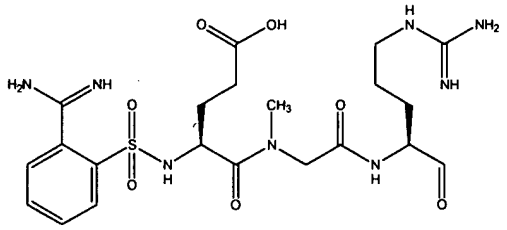
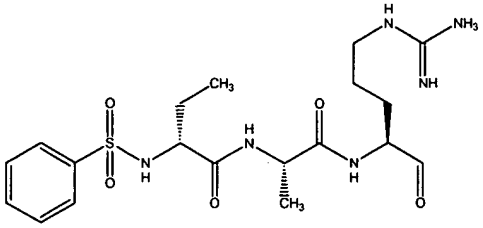
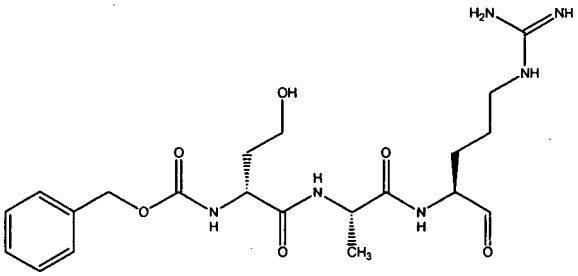
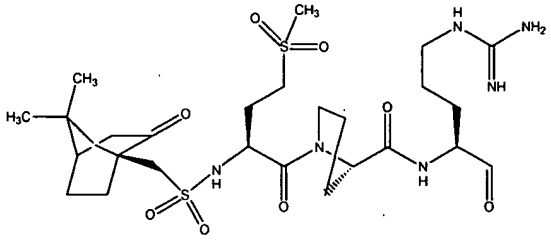
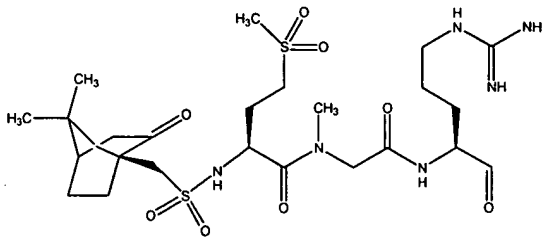
(12)  ;

(13)  ;

(14)  ;

(15)  ;

(16) 

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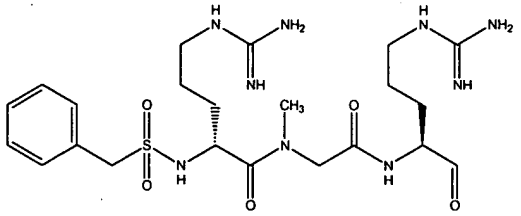
(17) 

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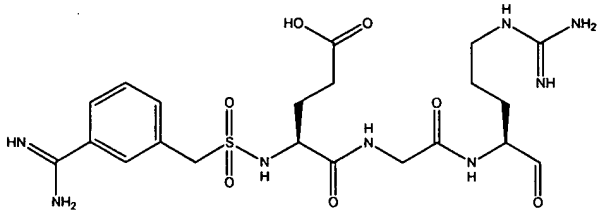
(18) 

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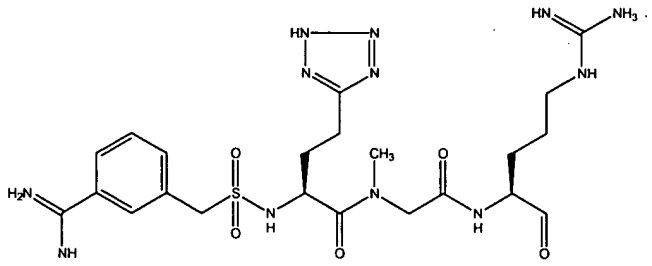
(19) 

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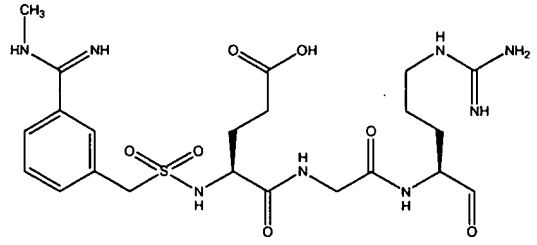
(20) 

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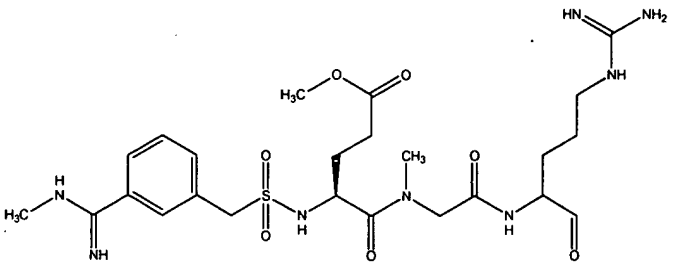

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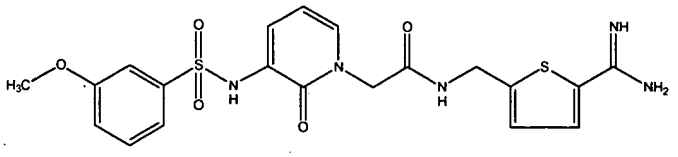

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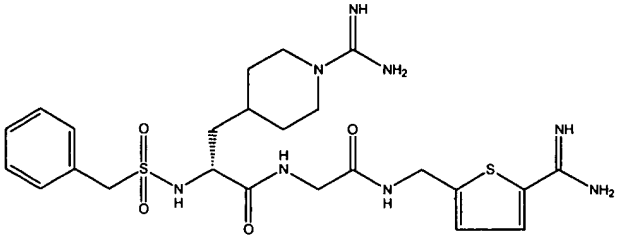

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2. (Amended) A method according to claim 1 wherein said compound has an IC_{50} for inhibition of serine protease activity of matriptase or membrane-type serine protease 1 of 100 nM or less.

[3. A method according to claim 1 wherein said compound is selected from the compounds depicted in Figures 1A, 1B and 1C.]

4. (Amended) A method of treating a condition which is ameliorated by inhibiting or decreasing serine protease activity of matriptase or [MTSP1] membrane-type serine protease 1 in a mammal in need of treatment which comprises administering to said mammal a therapeutically effective amount of a compound which selectively inhibits serine protease activity of

matriptase or [MTSP1] membrane-type serine protease 1 wherein said compound is selected from the group consisting of:

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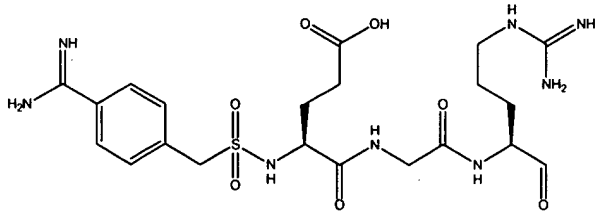

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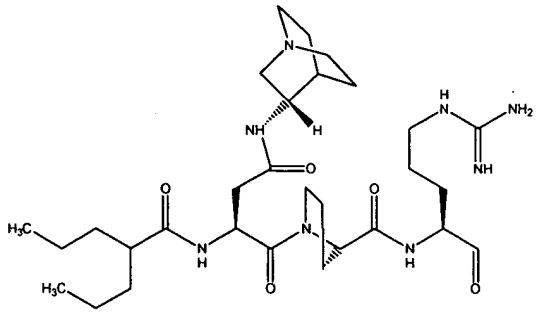

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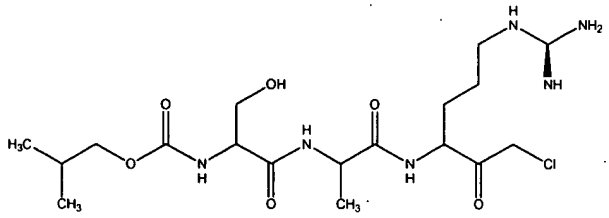

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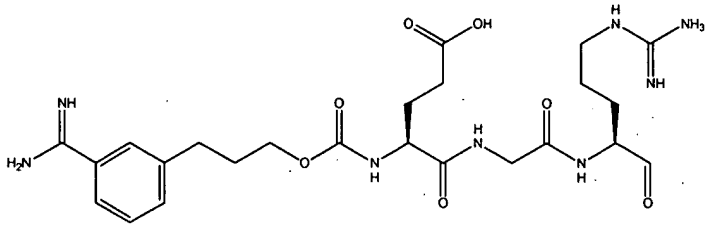

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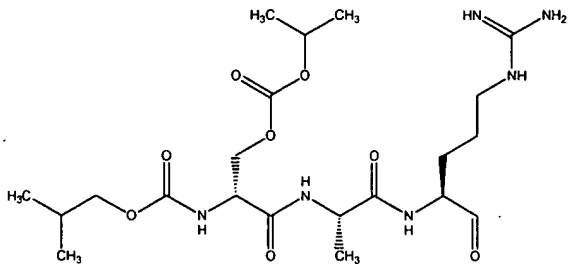

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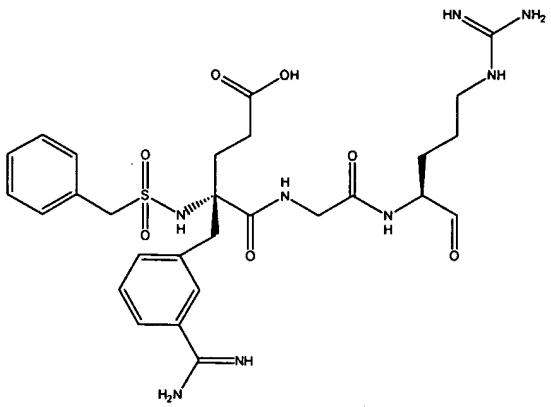

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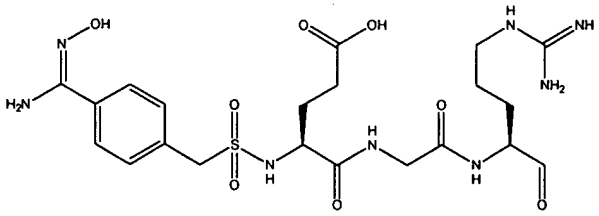

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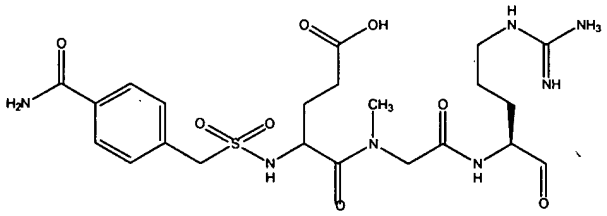

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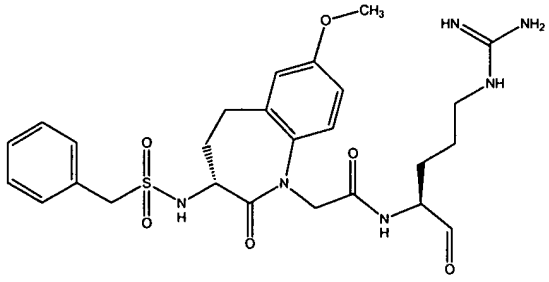

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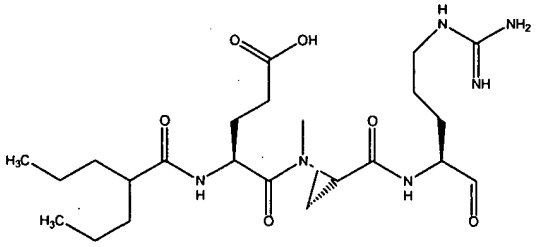

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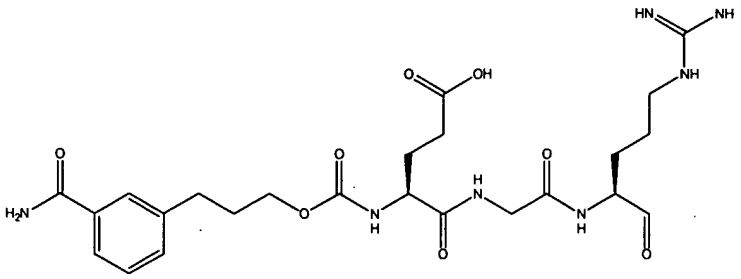

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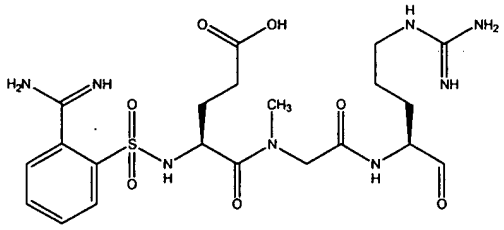

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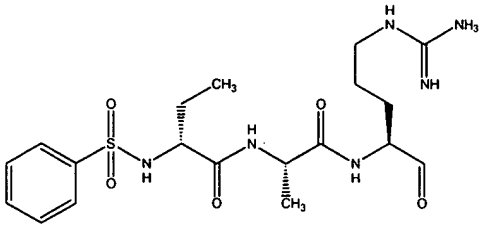

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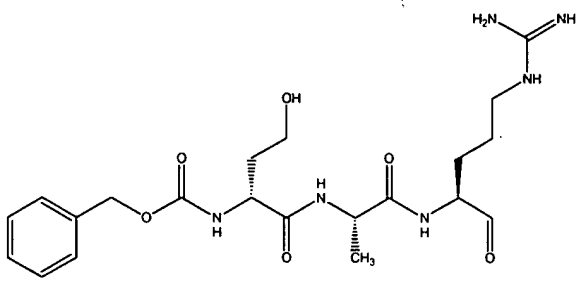

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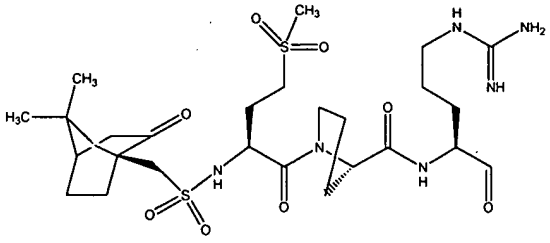

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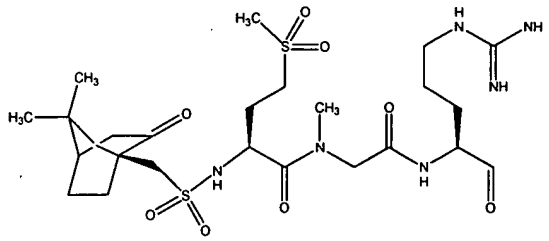
(16) 

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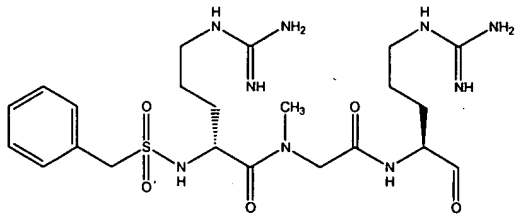
(17) 

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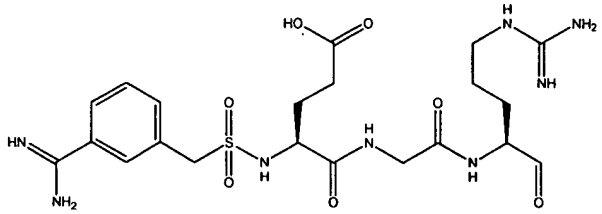
(18) 

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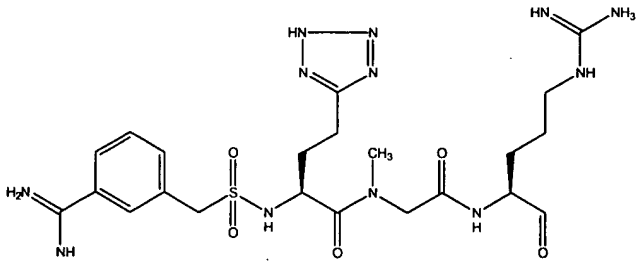
(19) 

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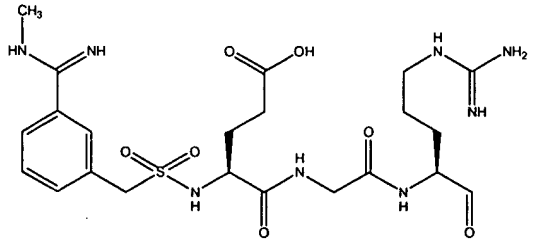
(20) 

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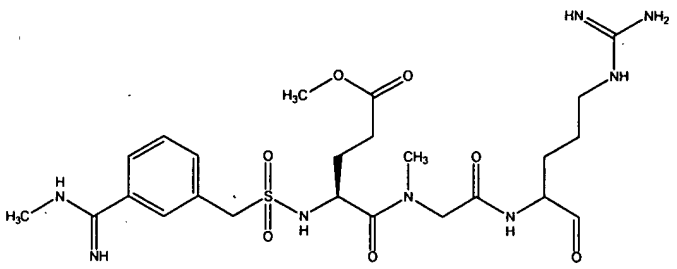
(21)



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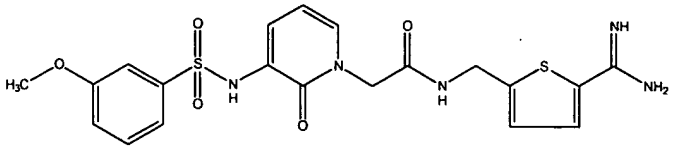
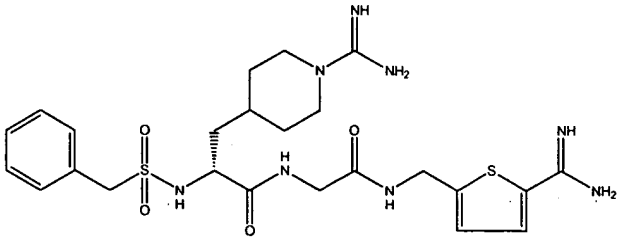


; and

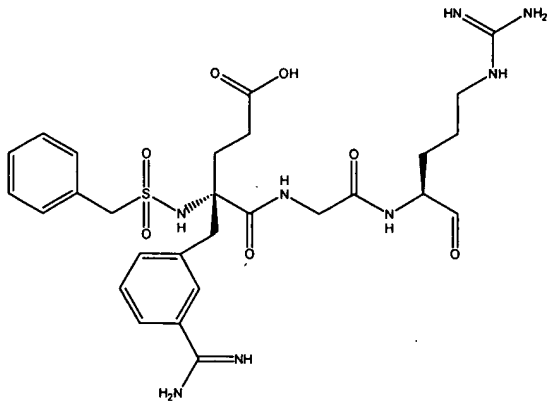
(23)



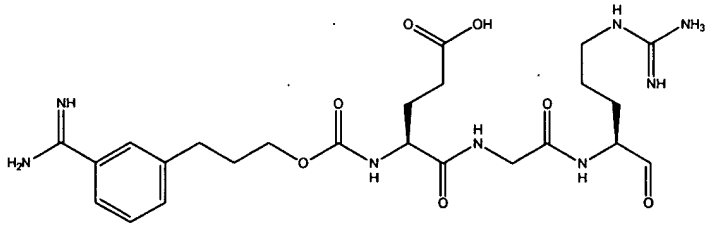
.

5. (Amended) A method according to claim 4 wherein said compound has an IC_{50} for inhibition of serine protease activity of matriptase or membrane-type serine protease 1 of 100 nM or less.

6. (Amended) The Compound [No. 6 of Figure 1A] of the formula:



7. (Amended) The Compound [No. 4 of Figure 1A] of the formula:



[8. A method of detecting a compound that inhibits serine protease activity of matriptase or MTSP1 which comprises contacting said compound with a peptide comprising a recombinant serine protease domain derived from matriptase or MTSP1 and a substrate and measuring substrate hydrolysis.

9. A method according to claim 8 wherein said serine protease domain comprises SEQ. ID. NO. 2.

10. A method of screening for a compound having activity in inhibiting serine protease activity of matriptase or MTSP1 which comprises determining whether said compound inhibits

serine protease activity of a peptide comprising a recombinant serine protease domain derived from matriptase or MTSP1.

11. A method according to claim 10 wherein said peptide comprises SEQ. ID. NO. 2 or an amino acid sequence having serine protease activity and at least about 80% sequence identity to SEQ. ID. NO. 2.

12. A method of screening a compound for activity in inhibiting serine protease activity of matriptase or MTSP1 which comprises determining whether said compound inhibits serine protease activity of a peptide comprising a recombinant serine protease domain comprising SEQ. ID. NO. 2 or an amino acid sequence having serine protease activity and at least about 80% sequence identity to SEQ. ID. NO. 2.

13. A recombinant serine protease domain derived from matriptase or MTSP1 which comprises SEQ. ID. NO. 2 or an amino acid sequence having serine protease activity and at least about 80% sequence identity to SEQ. ID. NO. 2.

14. A recombinant serine protease domain which comprises SEQ. ID. NO. 2.

15. A recombinant serine protease domain which comprises SEQ. ID, NO. 2 or an amino acid sequence having serine protease activity and at least about 80% sequence identity to SEQ. ID. NO. 2.]